**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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*Ex parte* PETER HOFERT and THOMAS BACKENSFELD

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Appeal 2007-2722
Application 09/807,402
Technology Center 1600

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Decided: December 13, 2007

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Before DONALD E. ADAMS, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* FREDMAN.

Opinion Dissenting filed by *Administrative Patent Judge* GRIMES.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a compositions of gestagens and cyclodextrin. In addition, there are claims to methods for making and stabilizing such compositions, which the Examiner has rejected on grounds of obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

## BACKGROUND

"Gestagens are used for the treatment of menopausal symptoms. Fertility can also be controlled with these gestagens." (Specification 1). The Specification discloses that "[g]estagens with an α-hydroxyketone structure in the side chain are subject to an acyloin rearrangement during storage" (*id.*).

According to the Specification "[c]omplexes that consist of steroidal sex hormones and cyclodextrin are known from WO 96/02277 (date of application: July 10, 1996). Only the complex that consists of 17α-ethinylestradiol and β-cyclodextrin is actually described" (*id.*).

Appellants teach regarding the invention that "[t]he object is thus to protect gestagens, especially (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione, from decomposition by acyloin rearrangement or oxidation without having a negative effect on the pharmacological compatibility and pharmaceutical processing. The object is achieved by a combination that consists of at least one gestagen and a β-cyclodextrin or γ-cyclodextrin" (*id.* at 2).

## STATEMENT OF THE CASE

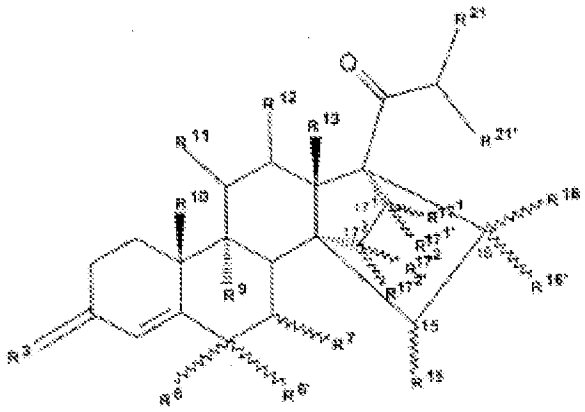
*The Claims*

Claims 2-5, 7, 10, 11, 13-16, 18-20, 22 and 23 are on appeal.

The claimed subject matter is reflected in representative claims 2 and 23, which read as follows[1]:

[1] Claims 2, 22 and 23 are the only independent claims before us. Claim 22 and the dependent claims were not separately argued.

2. A combination comprising at least one gestagen and a β-cyclodextrin or γ-cyclodextrin or a derivative of β-cyclodextrin or γ-cyclodextrin, which is obtained by etherification or esterification of free alcoholic functions of cyclodextrin, wherein said at least one gestagen is a compound of formula I:



(I)

in which

$R^3$ is an oxygen atom, a hydroxyimino group, or two hydrogen atoms,

$R^6$ is a hydrogen, fluorine, chlorine or bromine atom or an α- or β-position $C_1$-$C_4$ alkyl radical, wherein $R^{6'}$ and $R^7$ represent hydrogen atoms, or else

$R^{6'}$ is a hydrogen, fluorine, chlorine or bromine atom or a $C_1$-$C_4$ alkyl radical, wherein $R^{6'}$ and $R^7$ represent a common additional bond,

$R^7$ is an α- or β-position $C_1$-$C_4$ alkyl radical, wherein $R^6$ and $R^{6'}$ represent hydrogen atoms, or else

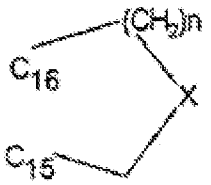
$R^6$ and $R^7$ together stand for an α- or β-position methylene group, and $R^{6'}$ is a hydrogen atom, or $R^6$ and $R^{6'}$ together stand for an ethylene group or a methylene group, and $R^7$ is a hydrogen atom,

$R^9$ and $R^{10}$ in each case stand for a hydrogen atom or a common bond,

$R^{11}$ and $R^{12}$ in each case stand for a hydrogen atom or a common bond,

$R^{13}$ is a methyl or ethyl group,

$R^{15}$ is a hydrogen atom or a $C_1$-$C_3$ alkyl radical,
$R^{16}$ and $R^{16'}$, independently of one another, stand for a hydrogen atom, a $C_1$-$C_3$ alkyl radical or a $C_2$-$C_4$ alkenyl radical or together for a $C_1$-$C_3$ alkylidene group,
$R^{15}$ and $R^{16}$ stand for a common bond, and $R^{16'}$ stands for a hydrogen atom or a $C_1$-$C_3$ alkyl radical, or
$R^{15}$ and $R^{16}$ together stand for a ring of partial formula




in which n = 1 and 2, and X means a methylene group or an oxygen atom, and $R^{16'}$ stands for a hydrogen atom,
$R^{171}$ is a hydrogen atom or a $C_1$-$C_3$ alkyl radical,
$R^{172}$ is a hydrogen atom, a $C_1$-$C_3$ alkyl radical, or a $C_2$-$C_4$ alkenyl radical,
$R^{171'}$ and $R^{172'}$ in each case is a hydrogen atom or for a common bond,
$R^{21}$ is a hydrogen atom or a $C_1$-$C_3$ alkyl radical,
$R^{21'}$ is a hydroxy group.

23. A method for stabilization of a gestagen from acyloin rearrangement comprising mixing said gestagen with a β-cyclodextrin or a γ-cyclodextrin or a derivative of a β-cyclodextrin or a γ-cyclodextrin, which is obtained by etherification or esterification of free alcoholic functions of cyclodextrins, wherein said gestagen is a compound of formula I [i.e., the same compound defined in claim 2].

The Examiner has rejected claims 2-5, 7, 10, 11, 13-16, 18-20, 22 and 23 under 35 U.S.C. § 103(a) based on:

Backensfeld et al. U.S. Patent 5,798,338, August 25, 1998 (hereafter "Backensfeld").

Schollkopf et al. WO 96/20209, July 4, 1996 (hereafter

"Schollkopf"). Citations to this reference will be drawn to the translation.

Hedges, Allan R. "Industrial Applications of Cyclodextrins" 98 Chemical Reviews 2035-2044 (June 25, 1998).

*The Issues*

The Examiner's position is that Backensfeld discloses generic combinations of gestagens with cyclodextrin for reasons including improved bioavailability, improved solubility and reduced oxidative degradation (Answer 4, 6). The Examiner states that Schollkopf teaches specific gestagens including the specific species of gestagens which are claimed (Answer 3). The Examiner points to Hedges as further support for teaching the use of cyclodextrins in stabilizing and solubilizing pharmaceutical products (Answer 4). The Examiner concludes that the properties of improved bioavailability, solubility, and reduced oxidative degradation represent reasons to use cyclodextrin with the specific gestagens of Schollkopf (Answer 6).

Appellants respond that the gestagens of Backensfeld do not contain acyloin groups and are therefore not susceptible to acyloin rearrangement (App. Br. 3). Appellants further assert that they have shown an unexpected stabilization of ZK 187226 by cyclodextrins when combined with excipient (App. Br. 4-5). Appellants separately argue claim 23 noting "[a]dditionally, independent claim 23 drawn to a method for stabilization of a gestagen from acyloin rearrangement is not taught or suggested by the prior art as this problem was not even recognized by the prior art" (App. Br. 5).

In view of these conflicting positions, we frame the issues before us as follows:

(1) Would it have been prima facie obvious to one of ordinary skill in the art to combine the acyloin containing gestagens of Schollkopf with cyclodextrin in view of Backensfeld's generic teaching to combine gestagens with cyclodextrin and Hedges' teaching of the advantages of cyclodextrin?

(2) If these claims are prima facie obvious, does Appellants' reliance on the comparative data disclosed in their Declarations overcome the Examiner's prima facie case?

*Findings of Fact*

1. Backensfeld teaches combinations of steroids and cyclodextrin, noting "dosage forms are prepared that contain powdery cyclodextrin clathrates of these active ingredients" (Backensfeld, col. 1, ll. 31-33).

2. Backensfeld teaches combinations with α, β and γ cyclodextrins, indicating preference for "especially β-cyclodextrin" (*see* Backensfeld, col. 2, ll. 8-30).

3. Backensfeld teaches suitable gestagens for combination with cyclodextrin may, for example, include norethisterone, levonorgestrel, gestodene, desorgestrel, and 3-ketodesorgestrel (Backensfeld, col. 1, ll. 47-49).

4. Backensfeld provides three reasons for the preparation of solid dosage forms containing steroidal hormones combined with cyclodextrin. The first reason is "[i]n the preparation of such low-dosed dosage forms, strong fluctuations of the active ingredient concentrations in the dosage units occur almost unavoidably (inadequate content uniformity), which manifest themselves more strongly, the smaller the amount of the active ingredient" (Backensfeld, col. 1, ll. 16-20).

5. Backensfeld's second reason to combine cyclodextrin with gestagens is that "[i]n the storage of such low-dosed preparations, moreover, a reduction in the active ingredient concentration is often additionally observed as a result of, in most cases, oxidative degradation reactions of the active ingredient" (Backensfeld, col. 1, ll. 21-24).

6. Backensfeld's third reason to combine cyclodextrin with gestagens is that when steroidal sex hormones are put in low dosage preparations, "the bioavailability of the active ingredient is subject to a pronounced first-pass effect and exhibits great inter- and intra-individual fluctuations" (Backensfeld, col. 1, ll. 25-27).

7. Schollkopf teaches that "[i]n the gestagen receptor bonding test on gestagenic action using cytosol from rabbit uterus homogenate and $^{3}$H-progesterone as the reference substance, the new compounds reveal a very strong affinity to the gestagen receptor. In the pregnancy maintenance test on rat, the inventive compounds of the general formula (I) have a very high gestagenic effect" (Schollkopf 6, ll. 10-15).

8. Schollkopf teaches acyloin containing gestagens (*see* Schollkopf 5, ll 26-30).

9. Hedges teaches that the state of the art in cyclodextrin technology is well understood (*see* Hedges 2040, col. 2, last two paragraphs).

10. Hedges teaches that one of the fundamental properties of cyclodextrins is that they "can be used to stabilize compounds" (*see* Hedges 2040, col. 2, l. 31).

*Discussion*

When determining whether the Examiner erred in rejecting claims as obvious, "[i]t is well settled that the PTO 'bears the initial burden of presenting a prima facie case of unpatentability. . . . However, when a prima facie case is made, the burden shifts to the applicant to come forward with evidence and/or argument supporting patentability'." *In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007).

*Prima facie case for claims 2 and 23*

Claim 2 is drawn to a product, which is the combination of a gestagen of Formula I with a β or γ cyclodextrin or derivative thereof. Claim 23 is drawn to a "method for stabilization of a gestagen from acyloin rearrangement" in which a gestagen of formula I is mixed with a β or γ cyclodextrin or derivative thereof. The only physical step of the claim, the mixing of a gestagen with an acyloin group with a β or γ cyclodextrin, is the formation of the product of claim 2.

We therefore initially turn our attention to the prima facie case of obviousness. We find that the Backensfeld patent specifically teaches the combination of gestagens in general with the same two types of cyclodextrin present in claim 2 (*see* FF 1-3). We also find that the Backensfeld patent provides a number of different reasons to add cyclodextrins to gestagens, including reduced fluctuations in dosage, stabilization against oxidative degradation, and improved bioavailability (*see* FF 4-6 and Answer 4, 6). We also find that Schollkopf identifies specific gestagens as effective in contraception, including gestagens that fall within the scope of the compounds of formula I as set forth in Appellants' claim 2 (*see* FF 7-8).

In analyzing the prima facie case of obviousness, the difference between the Backensfeld patent and the claimed invention is that the Backensfeld patent does not teach acyloin containing gestagens. It is Schollkopf who teaches acyloin containing gestagens which meet the requirements of formula I of claim 2.

"Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982); *see also In re Mayne*, 104 F.3d 1339, 1340 (Fed. Cir. 1997) ("[b]ecause the applicants merely substituted one element known in the art for a known equivalent, this court affirms [the rejection for obviousness]."). *Accord KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) ("when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result").

Applying the *Fout* and *KSR* standard of obviousness to the Examiner's findings and our findings of fact, we conclude that claims 2 and 23 would have been obvious to an artisan of ordinary skill (*see* FF 1-7). Claims 2 and 23 simply substitute certain specific known gestagens of Schollkopf into the composition of gestagens and cyclodextrins taught by the Backensfeld patent. Such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR Int'l*, 127 S. Ct. at 1740.

In the current case, the Specification is replete with references to preventing acyloin rearrangement by the addition of cyclodextrin (*see* Specification 2, 15). The entire tenor of Appellants' arguments throughout

prosecution revolve around this central goal of preventing acyloin rearrangement and Appellants argue here that the prevention of acyloin rearrangement renders the claims nonobvious (*see* App. Br. 3-5).

However, in *Woodruff*, the Federal Circuit analyzed the patentability of a process claim whose preamble was a "method of inhibiting fungal growth on refrigerated fresh fruits and vegetables". *In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990). The prior art was drawn to a "method of storing fresh leafy and head vegetables (such as lettuce) in order to 'maintain their fresh appearance ... even over extended periods of time.'" *Id.* at 1576. The patentee in Woodruff argued that since "the prior art did not recognize the fungi-inhibiting property of Woodruff's method, the prior art could not render obvious a method having the purpose of inhibiting fungal growth." *Id.* at 1577. The Federal Circuit responded that "we do not agree that what Woodruff has allegedly discovered and claimed can be termed a new purpose for performing the claimed method. The generic purpose of the method disclosed in McGill is to prevent the deterioration of fresh vegetables, which certainly encompasses the specific benefit disclosed by Woodruff." *Id.* at 1577.

Applying the *Woodruff* analysis to the instant facts, we find that while the Backensfeld patent did not recognize that β or γ cyclodextrins will prevent degradation by the specific path of acyloin rearrangement, a central purpose for which Backensfeld added cyclodextrin was to prevent oxidative degradation of the gestagen (*see* FF 5). A generic purpose of the Backensfeld patent was therefore to prevent degradation of any generic gestagens used in solid dosage forms, including known prior art gestagens

such as those of Schollkopf, in the pharmaceutical preparation (*see* FF 1-3, 5, 7-10).

The prior art was well aware of cyclodextrin as a stabilizing agent (*see* FF 10). Backensfeld taught that the addition of cyclodextrin to gestagens helped prevent oxidative degradation, (see FF 5, 10). The *Woodruff* court concluded "[i]t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable. . . . While the processes encompassed by the claims are not entirely old, the rule is applicable here to the extent that the claims and the prior art overlap." *In re Woodruff*, 919 F.2d at 1578. We conclude that there is a prima facie case of obviousness for claims 2 and 23, since the prior art of Backensfeld, Schollkopf and Hedges suggest mixing the two components for three strong reasons, reduction of oxidative degradation, improved bioavailability, and improved dosage control (*see* FF 4-6).

*Analysis of Secondary considerations*

Having found a prima facie case of obviousness for claims 2 and 23, we next consider Appellants' rebuttal based upon secondary considerations. Appellants argue that the addition of cyclodextrin to gestagens with acyloin groups results in an unexpected result in that there is reduced acyloin degradation of these gestagens, when mixed with excipient (*see* App. Br. 3). Appellants have provided two declarations regarding these asserted unexpected results. In the November 4, 2004 Backensfeld Declaration, Dr. Backensfeld shows that the compound ZK 187226 has reduced acyloin rearrangement when in the presence of cyclodextrin (*see* Backensfeld Declaration). In the Backensfeld Declaration attached to the Appeal Brief

and dated May 31, 2006, Dr. Backensfeld explains three data tables from the June 16, 2005 amendment. Dr. Backensfeld argues that because ZK 187226 was stable when not combined with excipients, there would be no motivation to combine it with cyclodextrin. Dr. Backensfeld also shows that ZK 187226 degrades due to acyloin rearrangement when combined with "common excipients" and not complexed with cyclodextrin, but that cyclodextrin stabilizes ZK 187226.

The evidence is deficient for several reasons. First, no comparison of stability or decomposition was performed between the claimed compounds and the prior art compounds disclosed in Backensfeld. It is well settled that the comparison must be with the closest prior art, *In re De Blauwe*, 736 F.2d 699 (Fed. Cir. 1984); *In re Burckel*, 592 F.2d 1175 (CCPA 1979); and that the comparison must be commensurate with the scope of the claims, *In re Grasselli*, 713 F.2d 731 (Fed. Cir. 1983).

The acyloin degradation shown in the Backensfeld declaration shows, *inter alia*, the conversion of ZK 187226 to ZK187225 as the predominant degradation product (Backensfeld Declaration 11/4/04 at 2-3). This "acyloin rearrangement" is a type of racemization of ZK187226, where the chirality of the bond between the carbon and hydroxyl in the acyloin changes.

While the compounds of Backensfeld, which lacks the acyloin, could not undergo this particular racemization, there are numerous chiral centers in the gestagens disclosed by Backensfeld which could also undergo racemization (*see* Backensfeld, col. 1, ll. 47-49). In failing to compare whether the cyclodextrin clathrates which prevent racemization of ZK187226 also prevent racemization of the compounds in the closest prior

art of Backensfeld, the Declaration fails to show that the result was unexpected, particularly since Backensfeld teaches that cyclodextrin prevents degradation (*see* FF 5).

Separately, Appellants' argument regarding the different stabilities in the presence or absence of excipient fails to appreciate that the Backensfeld patent expressly teaches the use of excipients (see Backensfeld, col. 2, ll. 45-49). The argument that ZK187226 is stable in the absence of excipient does not address the true stability question, which is whether the gestagens of interest will be stable in the pharmaceutical preparation made in the Backensfeld patent. In Example 3, the Backensfeld patent expressly discloses a tablet made with a number of different excipients (see Backensfeld, col. 3, ll. 40-49). The declaration evidence does not perform a comparison using these excipients and other gestagens disclosed by the Backensfeld patent.

Second, the scope of the evidence is not commensurate with the scope of the claim. The evidence presented is for a single compound, ZK 187226 (see Backensfeld Declaration, 11/4/04 at 1-3). The genus of formula 1 includes R21 as hydrogen or a C1-C3 alkyl radical in the acyloin portion. Thus, even in the acyloin portion, there are multiple different enantiomers, and when calculating the total number of possible different molecules, not including enantiomers, encompassed by the claim, there are at least 13,212,057,600 possibilities (3 ($R^3$) x 12 ($R^6$) x 8 ($R^{6'}$) x 8 ($R^7$) x 2 ($R^9$) x 2 ($R^{10}$) x 2 ($R^{11}$) x 2 ($R^{12}$) x 2 ($R^{13}$) x 4 ($R^{15}$) x 10 ($R^{16}$) x 10 ($R^{16'}$) x 4 ($R^{171}$) x 7($R^{172}$) x 2 ($R^{171'}$) x 2 ($R^{172'}$) x 4($R^{21}$)).

This fact pattern is similar to that in *Greenfield*, where it was asserted that formaldehyde stabilizes isothiazolone from decomposition. *See In re Greenfield*, 571 F.2d 1185, 1188 (CCPA 1978). The CCPA found that "[e]stablishing that one (or a small number of) species gives unexpected results is inadequate proof, for 'it is the view of this court that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.'" *Id.* at 1189. The same deficiency is present in the current evidence, which only provides a showing of stabilization of a single, not specifically claimed compound, ZK 187226[2], in a genus much larger than that at issue in *Greenfield*.

Also, the conclusion of nonobviousness drawn by Dr. Backensfeld in the declaration fails to recognize additional reasons beyond the protection from degradation which might motivate the combination of gestagens with cyclodextrins, including improved solubility and bioavailability which provide additional reasons for forming the composition of claim 2 (*see* FF 4, 6).

We conclude that the secondary evidence provided by Appellants is insufficient to overcome the prima facie case because the data is not properly compared to the prior art and is not commensurate in scope with the claimed invention.

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[2] The structure of ZK187226 appears to be a stereoisomer of the gestagen of claim 3, but does not appear to be identical to the gestagen of claim 3. We agree with the dissent that ZK187226 falls within the formula of claim 2, but we disagree that there are only four possibilities for the acyloin group given that there is at least one chiral center and thus there will be stereoisomers as well.

The role of secondary considerations, such as unexpected results, may "serve to 'guard against slipping into use of hindsight,' . . . and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). The dissent argues that the secondary consideration of unexpected results rebuts the prima facie case. However, the mere presence of a secondary consideration is not solely dispositive, and in *Graham*, the Supreme Court found that "these factors do not, in the circumstances of this case, tip the scales of patentability." *Id.* at 36.

We are charged to review the evidence as a whole to establish whether the claims are obvious and not simply look to unexpected results as the sole arbiter of obviousness. *See, e.g. Pfizer v. Apotex*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

> In *Pfizer*, the Federal Circuit commented that
>
> we hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. Newell Cos., Inc. v. Kenney Mfg. Co., 864 F.2d 757, 768 (Fed.Cir.1988). Here, the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient.

*Pfizer* at 1372. We think the dissent places the unexpected results in control of the obviousness conclusion to the exclusion of the very strong prima facie case of obviousness in the current situation. Even if we credit Appellants' unexpected result that cyclodextrin reduces acyloin rearrangement in acyloin

containing gestagens, when we balance the fact that Backensfeld had already combined gestagens with cyclodextrin along with the three motivations of Backensfeld for adding cyclodextrin to gestagens: reducing oxidative degradation, improving bioavailability, and improving dosage control, we find the claims obvious.

In this case, where the record establishes a very strong case of prima facie obviousness in light of the Backensfeld and Schollkopf references, the unexpected result is insufficient to tip the scales of patentability and overcome the conclusion of obviousness.

SUMMARY

We affirm the rejections of claims 2 and 23 as obvious in view of Backensfeld in view of Schollkopf and further in view of Hedges. Pursuant to § 41.37(c)(1)(vii)(2006), we also affirm the § 103 rejection of claims 3-5, 7, 10, 11, 13-16, 18-20, 22, as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

GRIMES, *Administrative Patent Judge*, dissenting.

I agree with my colleagues that the references relied on by the Examiner support a prima facie case of obviousness. In my view, however, Appellants have overcome the prima facie case by providing evidence that the claimed combination and method have unexpectedly superior properties.

The Specification states that it was known in the prior art that "[g]estagens with an α-hydroxyketone structure in the side chain are subject to an acyloin rearrangement during storage. In this case, steric variants occur. This rearrangement is accelerated by many pharmaceutical adjuvants (e.g., lactose, magnesium stearate)." (Spec. 1-2.) The gestagens recited in the claims on appeal all have an α-hydroxyketone structure in the side chain, since $R^{21}$ is hydrogen or a $C_1$-$C_3$ alkyl radical and $R^{21'}$ is hydroxy. Thus, the evidence shows that those skilled in the art would have expected the gestagens recited in the claims to be subject to an acyloin rearrangement during storage and that the rearrangement would be accelerated by many pharmaceutical adjuvants.

Appellants have provided two declarations showing that combining a gestagen within the scope of formula I with β-cyclodextrin significantly reduces the amount of acyloin rearrangement that takes place during storage.[3] The declaration of Thomas Backensfeld submitted Nov. 4, 2004 ("2004 Declaration") shows the results of "[s]ide-by-side storage stability comparative tests of tablets containing ZK 187226 . . . without and with the presence of β-cyclodextrin in the tablets. . . . The tablets were stored for 1,5

[3] The majority asserts that ZK 187226 is "not specifically claimed," on the basis that it is a stereoisomer of the compound recited in claim 3 rather than the compound of claim 3 itself, but concedes that ZK 187226 is encompassed by formula I. *Ante* at 14, n.2.

months under a variety of conditions" of temperature and humidity (2004 Declaration, p. 1).

The 2004 Declaration includes an HPLC chromatogram showing that tablets containing ZK 187226 (without cyclodextrin) also contain a number of other compounds after 1.5 months storage under various conditions (2004 Declaration, p. 3). Some of the other compounds result from acyloin rearrangement (labeled peaks to the right of ZK 187226 in the chromatogram) and other compounds are uncharacterized (unlabeled peaks to the left of ZK 187226 in the chromatogram).

The 2004 Declaration also includes an HPLC chromatogram showing that tablets containing ZK 187226 in combination with β-cyclodextrin contain almost no degradation products after 1.5 months' storage (2004 Declaration, p. 4).

These results are presented numerically in Appellants' response received June 20, 2005, which are incorporated by reference into the declaration of Thomas Backensfeld attached to the Appeal Brief ("2005 Declaration"). The numerical results show that the ZK 187226-containing tablets without cyclodextrin include 2.0 to 41.2% acyloin rearrangement products and 2.2 to 97.3% other, uncharacterized degradation products (June 20, 2005 Response, p. 11; 2005 Declaration, p. 2). The tablets containing ZK 187226 and β-cyclodextrin, by contrast, contained only 0.1 to 0.7% acyloin rearrangement products and 1.0 to 5.0% other degradation products (June 20, 2005 Response, p. 12; 2005 Declaration, p. 2).

Dr. Backensfeld declares that "the results are significant and would not have been expected by those in this field from the disclosure of

Backensfeld or otherwise" (2004 Declaration, p. 5) and that the "significant reduction in acyloin rearrangement of ZK 187226 is unexpected from the prior art" (2005 Declaration, p. 2).

In my view, the declaratory evidence provides a sufficient showing of unexpected results to rebut the prima facie case of obviousness. "Mere improvement in properties does not always suffice to show unexpected results. . . . [H]owever, when an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995).

Here, the declaratory evidence shows a substantial improvement in stability of a gestagen-containing tablet with respect to acyloin rearrangement during storage when the gestagen is combined with β-cyclodextrin. Dr. Backensfeld also states that the results were unexpected from the prior art.

The evidence of record provides no basis for a contrary conclusion. The Specification discloses that gestagens containing an α-hydroxyketone structure are subject to both acyloin rearrangement and oxidation (Spec. 1-2). The Backensfeld patent discloses that combining gestagens with cyclodextrins prevents oxidative degradation "at least to a large extent" (Backensfeld, col. 1, ll. 21-33) but does not mention acyloin rearrangement.

Acyloin rearrangement is not oxidative degradation, since the resulting compounds are not oxidized with respect to the starting material. Thus, at best, the Backensfeld patent would have led those skilled in the art to expect that combining ZK 187226 with β-cyclodextrin would decrease the

amount of uncharacterized degradation products (those to the left of ZK 187226 in the chromatograms of the 2004 Declaration) but would not have led the skilled artisan to expect a decrease in acyloin rearrangement products.

Thus, in my view, the evidence meets the standard set out in *Soni* to establish unexpected results that overcome the prima facie case of obviousness.

The majority, however, concludes that the declaratory evidence is "deficient for several reasons" (*ante* at 12). First, the majority notes that the Backensfeld declarations do not include a comparison to the compounds of the Backensfeld patent. According to the majority, this omission is significant because acyloin rearrangement is a type of racemization[4] and the declaration does not address whether cyclodextrin prevents racemization of the other chiral centers in the compounds in the Backensfeld patent (which do not contain the α-hydroxyketone structure that leads to acyloin rearrangement) (*id.* at 13).

The lack of a comparison to the compounds in the Backensfeld patent is irrelevant, for two reasons. First, the point of the declarations is to show an unexpected effect of β-cyclodextrin in preventing acyloin rearrangement, not preventing all chemical reactions that can occur during storage. The compounds disclosed in the Backensfeld patent lack the α-hydroxyketone

[4] Acyloin rearrangement is not, strictly speaking, "a type of racemization": it results in a mixture of compounds, two of which are racemates of a chiral center (such as the carbon bearing $R^{21}$ and $R^{21'}$ in formula I) and two of which result from the α-hydroxy group and the carbonyl oxygen switching positions.

structure that leads to acyloin rearrangement and therefore no useful purpose would be served by a comparison involving those compounds.

Second, the Backensfeld patent only discloses that cyclodextrin prevents oxidative degradation of gestagens. Thus, even if β-cyclodextrin were found to inhibit racemization at other chiral centers of the gestagens disclosed in the Backensfeld patent, that result would not cast doubt on Appellants' unexpected results evidence, but provide further evidence of unexpected superiority of the claimed combination.

The majority also argues that the evidence of unexpected results is not commensurate with the scope of the claims, because formula I encompasses 13,212,057,600 different compounds (*ante* at 13-14). I will accept my colleagues' arithmetic for argument's sake, but in my view most of the variability allowed by formula I is unimportant. The declaratory evidence is directed to the effect of β-cyclodextrin on acyloin rearrangement, which affects only the substituents in the $R^{21}$ and $R^{21'}$ positions (see the 2004 Declaration, p. 2). Claim 1 requires that $R^{21'}$ be a hydroxy group and that $R^{21}$ be either hydrogen or a $C_1$-$C_3$ alkyl radical. Thus, with regard to the part of the gestagen affected by acyloin rearrangement, the claims encompass only *four* possibilities, one of which is shown in the declaratory evidence.

Evidence of unexpected results is "commensurate in scope" with a claim if the evidence provides a reasonable basis for concluding that the untested embodiments encompassed by the claim would behave in the same manner as the tested embodiment(s). *See In re Lindner*, 457 F.2d 506, 508 (CCPA 1972) ("Here, only one mixture of ingredients was tested. . . . The claims, however, are much broader in scope, . . . and we have to agree with

the Patent Office that there is no 'adequate basis for reasonably concluding that the great number and variety of compositions included by the claims would behave in the same manner as the [single] tested composition.'" (bracketed material in original)).

In this case, neither the majority nor the Examiner has provided any evidence that different substituents in the other R positions of formula I would be expected to affect acyloin rearrangement. Therefore, neither the majority nor the Examiner has provided any basis for concluding that the results shown in the declarations for compound ZK 187226 would not be representative of the effect of β-cyclodextrin on other compounds encompassed by formula I.

In summary, I agree with the Examiner and my colleagues that the prior art supports a prima facie case under 35 U.S.C. § 103, but in my view Appellants' evidence of unexpected results effectively rebuts the prima facie case. I would reverse the rejection.

Ssc:

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201